Oral Oncology 88 (2019) 124–130

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Extranodal extension is a criterion for poor outcome in patients with metastatic nodes from cancer of the nasopharynx

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ARTICLE INFO

Keywords:
Extranodal extension
Nodal staging
Head and neck cancers
Nasopharyngeal cancer
Magnetic resonance imaging

ABSTRACT

Purpose: Extranodal extension (ENE) is a criterion for advanced nodal staging of oropharyngeal and hypopharyngeal carcinoma. Our aim was to determine if ENE should be a staging criterion for nasopharyngeal carcinoma (NPC).

Materials & methods: MRI of 546 NPC patients were reviewed retrospectively and in 404/546 (74.0%) with metastatic nodes, the nodes were assessed for ENE (grade 0 = absent; grade 1 = infiltration of surrounding fat; grade 2 = infiltration of muscle/skin), size (total volume), site (unilateral/bilateral and upper/lower neck) and necrosis. Associations between nodal features and regional relapse free survival (RRFS), distant metastases free survival (DMFS) and overall survival (OS) were assessed using cox regression. Differences of survival rates were compared using log-rank test. A p-value of < 0.05 indicates statistical significance.

Results: ENE grade was the only determinant of RRFS ($p = 0.014$) and only independent determinant of DMFS ($p = 0.003$) and OS ($p < 0.001$). Grade 2 ENE was associated with significantly poorer RRFS, DMFS and OS compared to grade 0 and 1 ($p < 0.05$). Addition of grade 2 ENE to N1 and N2 disease showed similar poor RRFS, DMFS and OS to N3 disease ($p > 0.05$). Compared to the current stage N3 disease, inclusion of grade 2 ENE increased the number of N3 patients from 53/546 (9.7%) to 82/546 (15.0%) with similar hazard ratios for DMFS (6.855 and 7.125, respectively) and OS (3.614 and 4.085, respectively).

Conclusion: Grade 2 ENE (into muscle and/or skin and/or salivary glands) is an independent indicator of poor outcome and may be considered as a new criterion for N3 nodal disease in NPC.

Introduction

Extranodal extension (ENE) is a strong prognostic indicator of poor outcome in patients with metastatic nodes from head and neck cancer [1–4]. In the most recent edition of the cancer staging manual (8th edition), ENE was included as a new criterion for staging advanced nodal disease (N3) for cancers of the oropharynx and hypopharynx, but was not included as a new criterion for cancer of the nasopharynx [5,6].

Metastatic nodes from nasopharyngeal carcinoma (NPC) have long been associated with poor outcome, especially stage N3 disease which comprises bulky nodes (> 6 cm) or nodes in the lower neck [7,8]. However, despite the propensity of NPC to spread to nodes in the neck [9,10], and relatively high incidence of ENE (between 33.6% and 39.8%) [11,12], there is only limited data on the prognostic value of ENE in NPC [11,12]. Furthermore, there are now studies that suggest other nodal features such as total nodal volume [13–15] and nodal necrosis [16–18] may contribute to the poorer survival rates found in patients with metastatic nodes from cancer of the nasopharynx.

This study evaluated ENE, using a simple grading system, together with nodal size, site and necrosis using MRI in patients with NPC. The aim was to identify nodal features with the strongest association with clinical outcome and determine if new nodal features should be

Abbreviations: ENE, extranodal extension; NPC, nasopharyngeal carcinoma; MRI, magnetic resonance imaging; AJCC, american joint committee on cancer; UICC, international union of cancer control; RRFS, regional relapse free survival; DMFS, distant metastases free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

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https://doi.org/10.1016/j.oraloncology.2018.11.007
Received 7 August 2018; Received in revised form 30 October 2018; Accepted 5 November 2018
Available online 24 November 2018
1368-8375/

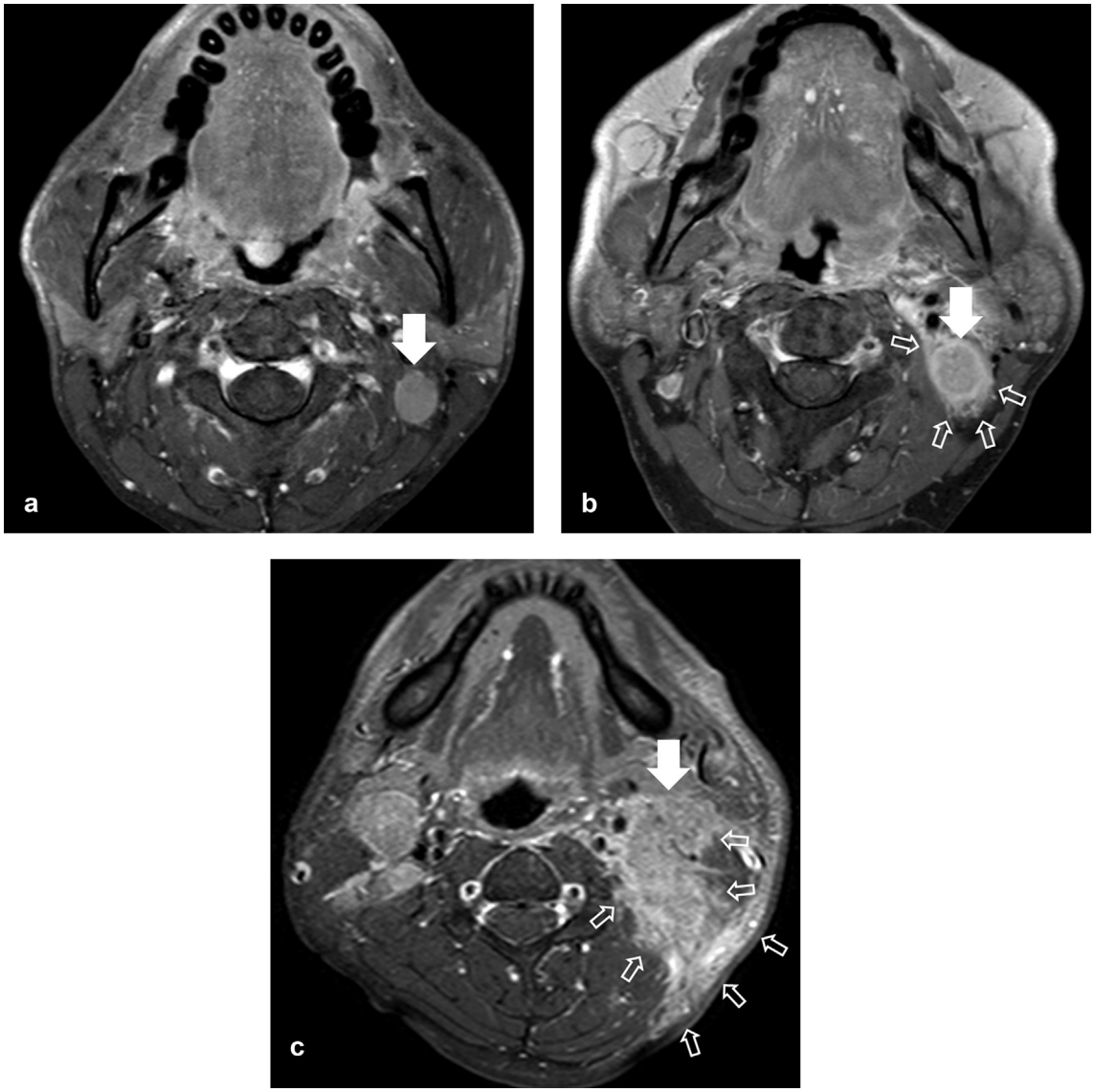

Fig. 1. Axial T1-weighted fat-suppressed contrast images of three NPC patients with metastatic neck nodes along the left internal jugular chain (large solid arrows). (a) shows a metastatic node without ENE (grade 0); (b) shows a metastatic node with early ENE infiltrating adjacent fat (small open arrows) (grade 1); (c) shows a metastatic node with advanced ENE infiltrating adjacent muscles and skin (small open solid arrows) (grade 2).

included in the advanced nodal stage (N3) for cancer of the nasopharynx.

Materials and methods

Patients

This was a retrospective local institutional review board approved study that recruited consecutive patients with newly diagnosed, non-disseminated, pathologically-proven NPC, who underwent a pre-treatment staging MRI examination of the head and neck at our institution between January 2005 and December 2012 and were treated with curative intent using intensity modulated radiotherapy with or without chemotherapy. Patients who were lost to follow-up or patients with a second primary tumour who developed distant metastases but the source of the distant metastases was uncertain, were excluded. Four hundred and sixty NPC patients in this study were included in a previous analysis of nodal volume [13].

Imaging

MRI examinations of the head and neck were performed on a 1.5 or 3.0 Tesla whole-body system (Philips Medical Systems, Best, The Netherlands). The protocol consisted of a minimum of an axial fat-suppressed T2-weighted sequence; an axial T1-weighted spin-echo sequence; axial and coronal T1-weighted spin-echo sequences with and without fat-suppression, following a bolus injection of gadoteric acid (Dotarem; Guerbet, Roissy, France) or gadolinium dimeglumine (Magnevist; Schering AG, Berlin, Germany). Sequences were obtained using a section thickness of 4 mm with no intersection gap, field of view of 23 cm, matrix varying from 256 to 800, and repetition and echo times dependent on the field strength and MRI sequence.

MRI analysis

MRI examinations were assessed by consensus by a researcher in NPC MRI (Q.Y.A.) and a radiologist (A.D.K.) specialised in head and neck MRI blinded to clinical outcome. The diagnosis of a metastatic node was based on recognized imaging criteria as follows: (1)

Table 1
Patient demographics, histology, T and N stage, overall stage and treatment in 546 patients.

	Number of patients (%)
Age (year)	
Mean ± standard deviation	52.7 ± 11.7 (range: 19–90)
Gender	
Male	424 (77.7%)
Female	122 (22.3%)
Histology types	
Undifferentiated carcinoma	526 (96.3%)
Poorly differentiated carcinoma	18 (3.3%)
Differentiated carcinoma	2 (0.4%)
T-category[#]	
T1	194 (35.5%)
T2	82 (15.1%)
T3	176 (32.2%)
T4	94 (17.2%)
N-category [#]	
N0	142 (26.2%)
N1	242 (44.6%)
N2	109 (20.0%)
N3	53 (9.7%)
verall stage[#]	
Stage I	52 (9.5%)
Stage II	155 (28.4%)
Stage III	203 (37.2%)
Stage IVA	136 (24.9%)
Chemotherapy	
Yes	382 (70.0%)
No	164 (30.0%)
Neoadjuvant	44 (8.1%)
Concurrent	382 (70.0%)
Adjuvant	11 (2.0%)

[#] T-category, N-category, and overall stage were classified according to the 8th AJCC/UICC cancer staging manual.

Table 2
ENS, nodal size, level, and necrosis in 404 patients with metastatic nodes.

Nodal features on MRI	Number of patients (%)
ENE	
Grade 0	251 (62.1%)
Grade 1	99 (24.5%)
Grade 2	54 (13.4%)
Nodal size	
Total nodal volume (cm^3)	19.53 ± 22.46* (range: 2.56–92.18)
Nodal laterality	
Unilateral	259 (64.1%)
Bilateral	145 (35.9%)
Nodal level	
Lower neck +	51 (12.6%)
Lower neck −	353 (87.4%)
Necrosis	
Necrosis +	109 (27.0%)
Necrosis −	295 (73.0%)
Total necrosis volume (cm^3)	0.38 ± 1.28* (range: 0–15.51)
Necrosis% (%)	7.22 ± 18.06* (range: 0–100)

ENE = extranodal extension.
* indicates mean value ± standard deviation.

retropharyngeal lymph nodes, cervical lymph nodes in the jugulodigastric region and any other cervical lymph nodes with a minimal axial diameter of 5 mm, 11 mm and 10 mm, respectively; (2) groups of three or more borderline lymph nodes with a minimal axial diameter of 8 mm; (3) lymph nodes of any size with ENE or necrosis [10,19]. Patients were staged according to the 8th edition of the American Joint Committee on Cancer (AJCC)/International Union of Cancer control (UICC) cancer staging guidelines [5,6]. Metastatic node were assessed for ENE, size, site, and necrosis on MR imaging according to the following methods:

ENE

ENE was assessed on the T1 weighted sequence post contrast with fat-suppression reference to the corresponding sequence (either T2-weighted or T1-weighted post contrast) [20]. ENE was classified into three grades: Grade 0, node without ENE (Fig. 1a); Grade 1, node with ENE infiltrating surrounding fat (Fig. 1b); and Grade 2, node with ENE infiltrating adjacent muscle and/or skin and/or salivary glands (Fig. 1c). ENE was excluded from analysis in metastatic retropharyngeal nodes that could not be clearly separated from local invasion from the primary tumour. The node with the highest grade of ENE was recorded.

Nodal size

Size was assessed using volume obtained by manually outlining the cross-sectional area of the node on each slice, summating the cross-sectional areas, and multiplying by the slice thickness of 4 mm. Total nodal volume was obtained by summating the volumes of all nodes (retropharyngeal and cervical nodes).

Nodal site

Nodal groups were divided based on laterality and level according to the current staging system [5,6]. For laterality the division was into unilateral or bilateral metastatic nodes and for level the division was into lower neck negative (lower neck −) and lower neck positive (lower neck +) using the landmark of the caudal border of the cricoid cartilage.

Nodal necrosis

Necrosis was identified as a focal area of high signal intensity on T2-weighted images or as an area of non-enhancement on contrast-enhanced T1-weighted images [21,22]. Necrosis was assessed for (1) presence of necrosis if at least one node showed necrosis (necrosis +) and absent if none of the nodes showed necrosis (necrosis −); (2) necrosis volume was obtained by manually outlining the necrosis in all nodes and summating the necrosis volume in all nodes (total necrosis volume) using the technique described above; (3) necrosis percentage (necrosis %) was obtained from the node with the maximum % necrosis (necrosis volume/total nodal volume × 100%).

Treatment and follow-up

The primary tumour and grossly enlarged lymph nodes received 66–74 Gray. Regions at risk of microscopic spread and the bilateral cervical lymphatics were selectively irradiated to 50–60 Gray. Overall stage I and II disease were treated by radiotherapy alone, while overall stages III and IV disease were treated by chemo-radiotherapy. The standard chemotherapy regime was concurrent mainly weekly low dose (40 mg/m^2) cisplatin [23] with or without neo-adjuvant or adjuvant chemotherapy. Patients were followed-up every 3–4 month in the first three years, 6 months in the fourth to fifth year, and then yearly.

Statistical analysis

Nodal features of ENE, size, site and necrosis were correlated with regional relapse free survival (RRFS), distant metastases free survival (DMFS) and overall survival (OS) using the cox regression. The RRFS, DMFS, and OS were measured from the start of treatment to the date of regional relapse, date of distant metastases, and date of death from any cause, respectively. The survival rate was calculated using the Kaplan-Meier analysis, and differences were compared using log-rank test. Significant parameters were added into the multivariate model. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated. ENS was graded again by the first observer (Q.Y.A.) and by a

Table 3
Analysis of nodal features and outcome in 404 patients with metastatic nodes.

	Univariate analysis						Multivariate analysis			
	RRFS		DMFS		OS		DMFS		OS	
	HR (95% CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
ENE grades		0.014*		< 0.001*		< 0.001*		0.003*		< 0.001*
Grade 0	1.000 (–)	–	1.000 (–)	–	1.000 (–)	–	1.000 (–)	–	1.000 (–)	–
Grade 1	1.569 (0.513–4.798)	0.429	1.326 (0.784–2.245)	0.293	0.723 (0.463–1.128)	0.153	1.096 (0.630–1.907)	0.744	0.637 (0.396–1.023)	0.062
Grade 2	4.783 (1.654–13.828)	0.004*	4.742 (2.956–7.605)	< 0.001*	2.672 (1.809–3.945)	< 0.001*	2.894 (1.503–5.573)	0.001*	1.989 (1.145–3.457)	0.015*
Total nodal volume	1.011 (0.994–1.028)	0.210	1.020 (1.014–1.026)	< 0.001*	1.012 (1.006–1.018)	< 0.001*	1.115 (0.600–2.073)	0.730	1.000 (0.990–1.010)	0.978
Uni/Bi-lateral nodes	2.234 (0.908–5.501)	0.080	1.996 (1.326–3.004)	0.001*	1.448 (1.044–2.009)	0.027*	1.206 (0.748–1.946)	0.442	1.179 (0.798–1.741)	0.409
Lower neck nodes (+/−)	1.003 (0.231–4.350)	0.996	2.764 (1.723–4.433)	< 0.001*	1.984 (1.314–2.997)	0.001*	1.245 (0.682–2.275)	0.475	1.293 (0.760–2.201)	0.343
Necrosis (+/−)	1.093 (0.393–3.035)	0.865	1.788 (1.169–2.734)	0.007*	1.597 (1.133–2.249)	0.007*	1.476 (0.828–2.631)	0.187	1.270 (0.797–2.024)	0.315
Total necrosis volume	1.097 (0.881–1.366)	0.409	1.045 (0.921–1.186)	0.492	1.062 (0.970–1.163)	0.191	–	–	–	–
Necrosis%#	1.947 (0.191–19.843)	0.574	3.031 (1.242–7.397)	0.015*	3.087 1.482–6.431	0.003*	0.831 (0.210–3.292)	0.792	1.471 (0.494–4.379)	0.488

RRFS = regional relapse free survival, DMFS = distant metastases free survival, OS = overall survival, HR = hazard ratio, CI = confidence interval, ENE = extranodal extension.
* indicates statistically significant.
\# indicates the maximum percentage of nodal necrotic volume of one single node.

second observer (A.D.K.) after an interval of one year. Intra- and inter-observer agreements for grading advanced ENE (grade 2) and non-advanced ENE (grade 0–1) was calculated using Cohen's kappa test and kappa coefficient was calculated. All statistical tests were two-sided, and a p-value of less than 0.05 was considered to indicate a statistically significant difference. All analyses were performed using the SPSS (24.0 version, IBM, NY, USA) statistical analysis software.

Results

Patient population

Five hundred and sixty patients were recruited of which 14 were excluded because they were lost to follow-up (n = 10) or had distant metastases that could have been from NPC or a second primary tumour (n = 4). Patients' demographics, tumour histology types, T and N category, overall stage, and treatment for the 546 patients included in this study are shown in Table 1. Metastatic nodes were present in 404/546 (74.0%). Median follow-up was 82.3 months (range: 3.2–150.0 months) with regional relapse in 22/546 (4.0%), distant metastases in 98/546 (17.9%), and death in 170/546 (31.1%); 5-year RRFS, DMFS, and OS were 96.5%, 83.1%, and 77.2%, respectively.

Association of nodal features and outcome in 404 patients with metastatic nodes

ENE, unilateral, bilateral, low neck nodes, and necrosis were present in 153/404 (37.9%), 259 /404 (64.1%), 145/404 (35.9%), 51/404 (12.6%) and 109/404 (27.0%) patients respectively, and mean total nodal volume was 19.53 ± 22.46 cm^3. Details of nodal features are shown in Table 2. Results of univariate analysis showed higher ENE grade, larger total nodal volume, bilateral nodes, lower neck +, necrosis + and higher necrosis% were associated poor DMFS and OS, and higher ENE grade was associated with poor RRFS (Table 3). Multivariate analysis of the significant nodal features showed ENE grades was the only nodal feature that remained significant for DMFS and OS (p = 0.003 and < 0.001, respectively) (Table 3).

Further analysis of ENE grades showed that patients with grade 2 ENE had significantly lower RRFS, DMFS and OS compared to grade 0 (all < 0.001) and grade 1 (p = 0.046, < 0.001, and < 0.001, respectively), while grade 0 and grade 1 had similar RRFS, DMFS and OS (p = 0.412, 0.301, and 0.153, respectively) (Fig. 2a–c).

The intra- and inter- observer class correlation coefficients (Kappa) for ENE grading were 0.884 and 0.830 respectively.

Prognostic value of adding advanced ENE (grade 2) into the current N3 staging system for all 546 patients

When patients were sub-grouped into non-advanced ENE (grade 0 and 1) and advanced ENE (grade 2), stage N1 and N2 nodes with advanced ENE (grade 2) were found to have similar RRFS, DMFS and OS to stage N3 disease (p = 0.784, 0.519, and 0.713, respectively) (Fig. 3a–c). Modifying the current 8th edition of the staging system by adding advanced ENE into N3 disease increased the number of patients with N3 disease from 53/546 (9.7%) to 82/546 (15.0%) and hence overall stage IVA from 136/546 (24.9%) to 158/546 (29.0%).

Patients with N3 disease using the current 8th edition and the modified 8th edition had a 5-year DMFS of 55.6% and 51.2% respectively (Supplemental Fig. 1a and b), and 5-year OS of 54.7% and 52.4% respectively (Supplemental Fig. 1c and d). To assess the hazard ratios of the current 8th edition and the modified 8th edition, multivariate analysis was performed adding confounding factors of age, gender, T category, overall stage and treatment (chemotherapy, yes or no). Results showed that the N-category in both the current 8th edition and the modified 8th edition of the staging systems were independent factors for DMFS and OS (Table 4). Compared to the current 8th edition, adding advanced ENE to N3 produced a slight increase in the HRs for DMFS (6.855 and 7.125 respectively), and OS (3.614 and 4.085

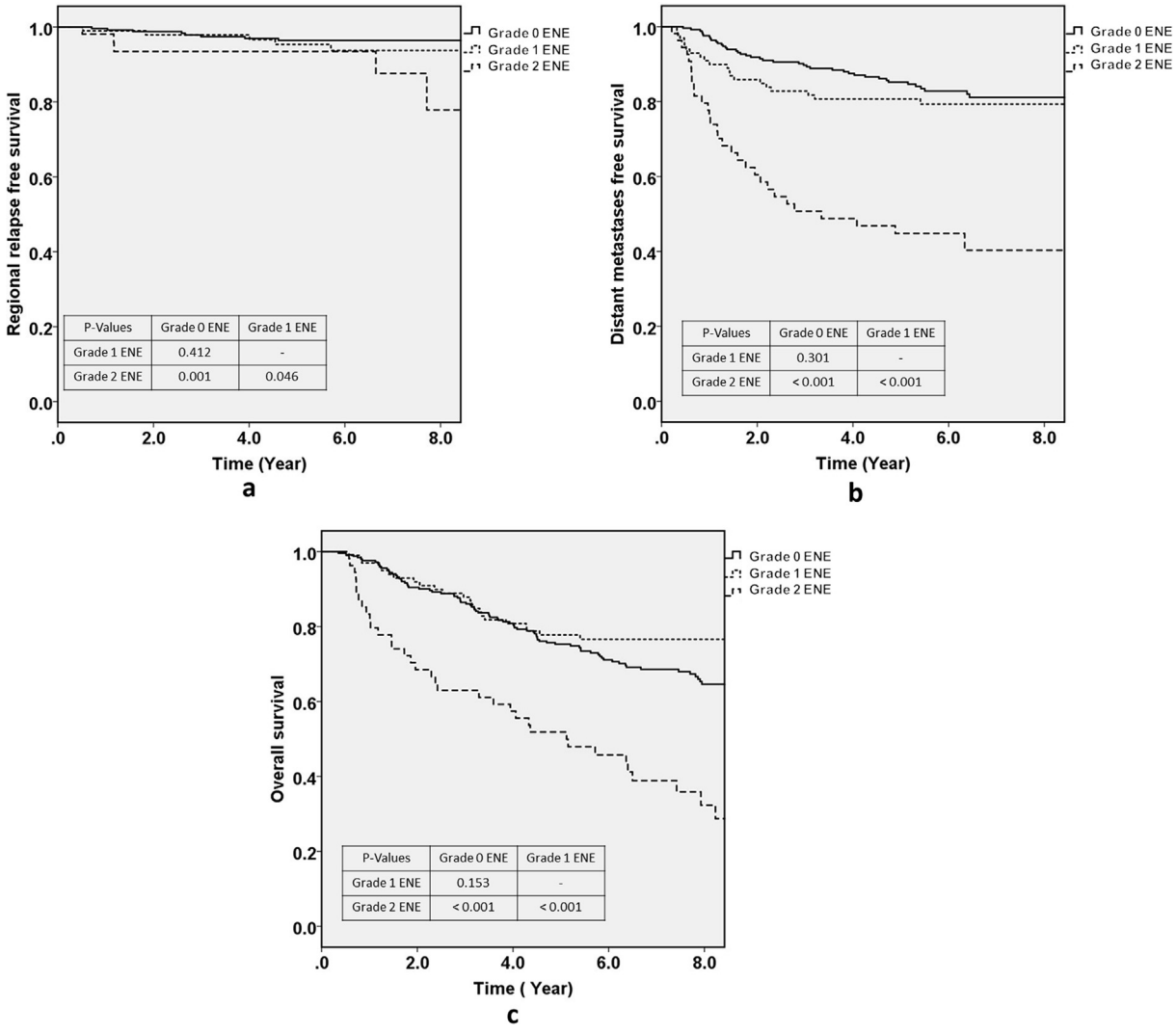

Fig. 2. The Kaplan-Meier curves of RRFS (a), DMFS (b) and OS (c) of three ENE grades (grade 0 to 2). NPC patients with metastatic nodes with grade 2 ENE had poorer outcome compared to grade 0 ENE and grade 1 ENE, while grade 0 ENE and grade 1 ENE had similar outcome.

respectively) (Table 4). Neither the N-category in the current 8th edition nor the modified 8th edition of the staging system was an independent factor for RRFS ($p = 0.141$ and 0.299, respectively).

Discussion

Nodal metastases are an important determinant of tumour progression in human cancers [24] and have a strong association with distant metastases [24]. However, few studies have tried to evaluate which of the morphological features of nodal metastases are responsible for the poor outcome. We evaluated all the main nodal features in one MRI study and found ENE was the only independent predictor of RRFS, DMFS and OS. ENE has been shown to relate to the overexpression of factors such as the epidermal growth factor receptor gene and matrix metalloproteinases [2], which contribute to disease progression in head and neck cancers, including NPC [25].

ENE cannot be accurately assessed by clinical examination and unlike many other head and neck cancers the pathological specimen is not available in NPC because the primary treatment is radiotherapy/chemo-radiotherapy rather than surgery. Therefore, imaging is the most accurate method to assess ENE in this cancer. We found about 40% of nodes showed ENE and most ENE was confined to the fat, although this infiltration could travel fairly long distances along the fat planes between the muscle groups. On the other hand, frank invasion of the muscles and into the skin was less frequent. We found it was important to grade ENE by MRI for prognostic purposes and we were able to accomplish this using a simple three grade system. Grading showed advanced ENE (grade 2) in which there was nodal extension into adjacent muscles and/or skin and/or salivary gland had much poorer RRFS, DMFS and OS than non-advanced ENE (grade 0 and 1) in which there was either no ENE or infiltration to surrounding fat only. The intra- and inter- observer agreements for grading advanced/non-advanced ENE by MRI showed high kappa coefficients. Pathological studies of other head and neck cancers have also shown the grade of ENE is important for predicting outcome [26–28]. Interestingly these studies showed metastatic nodes with advanced ENE had poorer outcome than those with early ENE or without ENE [26–28], which was in broadly in line with the grading system used in our study. Two previous MRI studies have assessed ENE in NPC and found conflicting results for the influence on outcome, but neither attempted to grade ENE [11,12].

Patients with advanced ENE (grade 2) in our study had a poor outcome which was similar to those with N3 disease, indicating advanced ENE (grade 2) has the potential to be a new imaging criterion for N3 disease. Modifying the current 8th edition staging system for N3 disease to include advanced ENE (grade 2) produced only a slight increase in the HRs but it allowed more patients (from 53 to 82 patients) to be upstaged to N3 disease and increased the number of patients with overall stage IVA. Our results suggest that the modified stage N3 disease

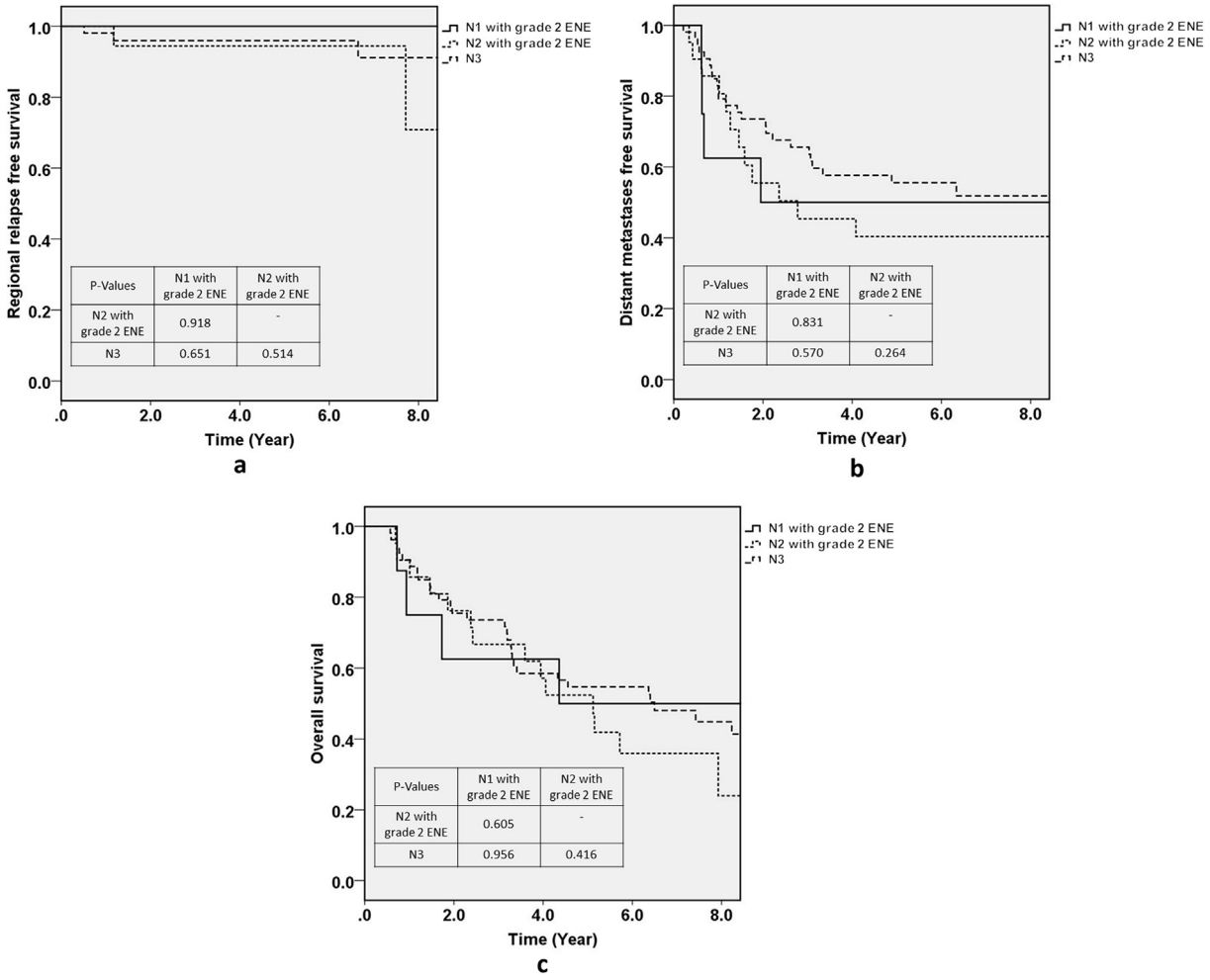

Fig. 3. The Kaplan- Meier curves of RRFS (a), DMFS (b) and OS (c) of stage N1 and N2 with grade 2 ENE, and stage N3 disease. The addition of grade 2 ENE to stage N1 and N2 disease had similar poor outcome to stage N3 disease.

Table 4
Current and modified nodal staging system to correlate with outcome in 546 patients.

	DMFS			OS		
	HR	95% CI	p-value	HR	95% CI	p-value
Current N staging system[#]			0.012*			0.002*
N0 (n = 142)	1.000	–	–	1.000	–	–
N1 (n = 242)	3.569	1.993–23.580	0.009*	2.345	1.329–4.137	0.003*
N2 (n = 109)	6.448	1.382–9.213	< 0.001*	3.300	1.761–6.183	< 0.001*
N3 (n = 53)	6.855	2.412–17.236	0.006*	3.614	1.400–9.329	0.008*
Modified N staging system by adding advanced ENE (grade 2) to the current stage N3 disease[#]			0.002*			0.004*
N0 (n = 142)	1.000	–	–	1.000	–	–
N1 (n = 234)	3.197	1.227–8.328	0.017*	2.232	1.259–3.955	0.006*
N2 (n = 88)	4.566	1.621–12.864	0.004*	2.690	1.371–5.276	0.004*
N3 (n = 82)	7.125	2.780–28.525	0.002*	4.085	1.823–9.155	0.001*

Notes: Age, gender, T-category, overall stage, and treatment (chemotherapy yes vs. no) were added into multivariate analyses.
ENE = extranodal extension, DMFS = distant metastases free survival, OS = overall survival, HR = hazard ratio, CI = confidence interval
[#] current staging system is classified according to the 8th AJCC/UICC cancer staging manual.
* indicates statistically significant.

may be used to select more patients who are at risk of a poor outcome. These patients could benefit from more aggressive treatment regimes [29,30], as well as whole body flurodeoxyglucose positron emission tomography-computed tomography at diagnosis to search for distant metastases and closer surveillance after treatment [31–33]. The inclusion of advanced ENE in the N3 nodal disease would also bring the N staging system for cancer of the nasopharynx more in line with those for cancers in the rest of the pharynx.

We also found nodal size, site and necrosis were predictors of outcome although none remained independent predictors after multivariate analysis. Larger nodal size, bilateral nodal metastases presence of low neck nodes, presence of necrosis and higher necrosis% were associated with poorer outcomes in our study. Unilateral nodes (N1), bilateral nodes (N2), low neck nodes (previously defined as

supraclavicular nodes and now defined as any nodes below the cricoid cartilage) are well established criteria for NPC nodal staging. Large nodes with a maximum nodal unidimension of > 6.0 cm is also a well-established criterion for staging N3 disease. In recent studies nodal volume has been investigated as an alternative indicator of size and has been found to be strongly associated with DMFS and OS [13–15]. Nodal volume may provide a better reflection of nodal size than a single unidimensional measurement, however, this measurement is time consuming and laborious to obtain. In our previous study, we found the main advantage of measuring volumes was for upstaging bulky N1 and N2 nodal disease that did not reach the 6 cm size criteria [13]. The impact of nodal necrosis on NPC outcome has also received little attention. We found the presence of necrosis in at least one node and high percentage of necrosis within an individual node predicted poor RRFS, DMFS and OS, similar to findings in previous studies [16–18]. However, none of these other nodal features (site, volume or necrosis) had an advantage over ENE as a nodal staging criterion.

There are some limitations in this study. First, the incidence of early ENE and mild necrosis (necrotic foci of < 3 mm) may be underreported on MRI compared to histology [20,22]. However, in regard to ENE the most advanced form of ENE (grade 2) was the most important prognostic indicator and this form of ENE is readily identified by MRI [34]. Second, we were unable to correlate nodal features with plasma EBV-DNA results because this blood test is not performed routinely in all our NPC patients. In addition, our results will need to be validated using an independent data set from other institutions.

Conclusion

Advanced ENE with infiltration into muscle and/or skin and/or salivary glands (grade 2) on MRI was the only nodal feature that predicted poor RRFS and only independent nodal feature that predicted poor DMFS and OS in patients with cancer of the nasopharynx. The addition of advanced ENE to the current criteria for the most advanced staging of nodal disease (N3) was able to increase the percentage of patients correctly predicted to have a poor outcome. These results suggest that advanced ENE graded by MRI has the potential to be an additional criterion for N3 disease which would bring the staging system for cancer of the nasopharynx more in line with that for staging cancers of the oropharynx and hypopharynx. However, further large-scale studies are needed to validate our findings.

Role of funding source

The work described in this paper was partially supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project No. SEG_CUHK02). The MRI scan is partially supported by this funding. The funding is not related to individual research project.

Conflict of interests

None declared.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.11.007.

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